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## Predictors of Outcome in Aneurysmal Subarachnoid Hemorrhage Patients

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Predictors of outcome in aneurysmal subarachnoid hemorrhage (aSAH) patients:

Observations from a contemporary multi-center dataset.

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Cover title: Predictors of outcome in aneurysmal SAH patients

Table 1

Table 2

Table 3

Table 4

Key words: aneurysmal subarachnoid hemorrhage, registries, outcome

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**Abstract:**

**Background:** The mortality and morbidity following aneurysmal subarachnoid hemorrhage (aSAH) has improved because of better diagnosis early treatment to secure the aneurysm, and better management of disease specific complications. With these improvements in care, it is not clear if the previously identified independent predictors of a negative outcome have changed. The aim of this study was to identify the independent predictors of an unfavorable outcome (Glasgow Outcome Score 1,2 & 3) in aSAH patients.

**Methods:** Univariate and multivariate analysis of prospectively collected data on patients presenting with an aSAH was performed. Outcome was assessed at discharge. Data were collected from 14 centers in the United Kingdom over a period of 4 years (September 2011-2015).

**Results:** The mean age (SD) at presentation of 3489 patients with aSAH was 55.3 (0.4). Most patients were female (n=2288 (68.5%)), presented in good grade (2397 (70%)) (World Federation of Neurological surgeons (WFNS) grade 1&2), and were treated by endovascular coiling (n=2600) (75%). The independent predictors of an unfavorable outcome (95% CI) were increasing age (OR 1.04, (1.03-1.05)  $p<0.001$ ), WFNS grade (OR 2.06 (1.91-2.22),  $p<0.001$ ) pre-operative re-bleeding (OR 7.41, (4.48-12.30)  $p<0.001$ ) need for CSF diversion (OR 3.25, (2.58-4.09)  $p<0.001$ ) and delayed cerebral ischemia (DCI) (OR 2.21, (1.72-2.83)  $p<0.001$ ).

**Conclusion:** These data suggest that potentially modifiable risk factors of pre-operative re-bleeding and DCI are associated with unfavorable outcomes. Understanding the reasons why patients requiring CSF diversion have 3.25-fold higher adjusted odds of a poor outcome at discharge needs to be studied.

## Introduction:

Advances in diagnostic and treatment strategies for aSAH; through the introduction of CT angiography with early detection of aneurysms; the use of nimodipine; specialist care for patients; and endovascular coiling of ruptured aneurysms, has substantially improved the outcomes of hospitalized patients{ ADDIN PAPERS2\_CITATIONS

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hiren.patel@srft.nhs.uk.</institution><subtype>400</subtype><endpage>60</endpage><bundle><publication><publisher>Elsevier B.V.</publisher><title>Clinical neurology and neurosurgery</title><type>-100</type><subtype>-100</subtype><uuid>0D39B70F-B5F9-42D0-9CA3-

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on>}. Despite these improvements SAH continues to exact a high economic and social cost.

It remains a disease of relatively young people (median age of presentation 52 years), and

causes a loss of productive life-years similar to that of ischemic stroke. Economically, the

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Although a number of factors have been identified as important in predicting outcome; poor presentation grade, increasing age, pre-protection aneurysm re-bleeding and delayed cerebral ischemia (DCI) are the only consistently identified independent predictors of a negative outcome in patients presenting with a subarachnoid hemorrhage (aSAH) { ADDIN

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</author><author><firstName>Peter</firstName><middleNames>J</middleNames><lastName>Kirkpatrick</lastName></author><author><firstName>Anil</firstName><middleNames>R</middleNames><lastName>Gholkar</lastName></author><author><firstName>Andrew</firstName><middleNames>J</middleNames><lastName>Molyneux</lastName></author><author><firstName>Donald</firstName><middleNames>M</middleNames><lastName>Shaw</lastName></author><author><firstName>Lynn</firstName><lastName>Copley</lastName></author><author><firstName>John</firstName><middleNames>P</middleNames><lastName>Browne</lastName></author><author><lastName>Steering Group for National Study of Subarachnoid

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cianokelly@hotmail.com</institution><number>4</number><subtype>400</subtype><endpage>801</endpage><bundle><publication><title>Journal of neurosurgery</title><type>-100</type><subtype>-100</subtype><uuid>7E633019-B1B0-46BA-BDA4-

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mes><lastName>Austin</lastName></author><author><firstName>M</firstName><middleNames>Christopher</middleNames><lastName>Wallace</lastName></author><author><firstName>David</firstName><lastName>Urbach</lastName></author></authors></publication></publications><cites></cites></citation>}. Most of the studies used to determine prognostic factors to date are limited by either a) being single center series b) including a predominance of patients treated by open microneurosurgery, or c) using a selected patient group randomized to clinical trials. Although most analyze and report on large prospective patient datasets, these data have been accumulated over a long period of time, and given the improvements in outcome seen over the last decade(s) we do not know if the independent predictors of outcome reported are still valid. Equally, we do not know if there are any new prognostic factors that can be modified to drive further improvements in care and outcome.

The aim of this study was to determine the independent predictors of a negative outcome in SAH patients from a contemporary dataset.

## **Materials and Methods.**

The analysis was conducted on patients that presented with an aneurysmal SAH (aSAH). Patient records were identified from the UK and Ireland SAH audit database ([{ HYPERLINK "http://www.hope-academic.org.uk/ukSAH/" }](http://www.hope-academic.org.uk/ukSAH/)) a prospective collection of anonymized data from aSAH treated in UK neurosurgical centres from September 2011-2015.

Demographic data (age, center, sex, presence of ischemic heart disease, hypertension, smoking status), severity of injury (WFNS (World Federation of Neurological Surgeons), aneurysm characteristics and treatments (aneurysm location, time to intervention, aneurysm treatment, need for CSF (cerebrospinal fluid) diversion, complications (CSF infection, re-bleed, delayed cerebral ischaemia (DCI)). Outcome was determined according to the

Glasgow Outcome Scale (GOS) at discharge. Discharge destination and length of stay were also recorded.

All data submitted was subject to the following pre agreed definitions in accordance with the standard operating policy of the database. CSF infection was defined as definite (if microbiologically proven) or probable (clinical signs and symptoms of CSF sepsis leading to clinician starting anti-microbial treatment). Presence of hypertension and ischaemic heart disease was determined from the past medical history provided by the patient or relatives on admission. WFNS grade was recorded at the time of referral to the neurosurgical center. DCI was defined as “The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (GCS) (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should not be apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies” { ADDIN

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m.d.vergouwen@amc.uva.nl</institution><number>10</number><subtype>400</subtype><endpage>2395</endpage><bundle><publication><title>Stroke; a journal of cerebral circulation</title><type>-100</type><subtype>-100</subtype><uuid>C3E45CC6-F627-47A0-B71B-7AEF50F1ED2E</uuid></publication></bundle><authors><author><firstName>Mervyn</firstName><middleNames>D I</middleNames><lastName>Vergouwen</lastName></author><author><firstName>Marinus</firstName><lastName>Vermeulen</lastName></author><author><nonDroppingParticle>van</nonDroppingParticle><firstName>Jan</firstName><lastName>Gijn</lastName></author><author><firstName>Gabriel</firstName><middleNames>J E</middleNames><lastName>Rinkel</lastName></author><author><firstName>Eelco</firstName><middleNames>F</middleNames><lastName>Wijdicks</lastName></author><author><firstName>J</firstName><middleNames>Paul</middleNames><lastName>Muizelaar</lastName></author><author><firstName>A</firstName><middleNames>David</middleNames><lastName>Mendelow</lastName></author><author><firstName>Seppo</firstName><lastName>Juvela</lastName></author><author><firstName>Howard</firstName><lastName>Yonas</lastName></author><author><firstName>Karel</firstName><middleNames>G</middleNames><lastName>Terbrugge</lastName></author><author><firstName>R</firstName><middleNames>Loch</middleNames><lastName>Macdonald</lastName></author><author><firstName>Michael</firstName><middleNames>N</middleNames><lastName>Diringer</lastName></author><author><firstName>Joseph</firstName><middleNames>P</middleNames><lastName>Broderick</lastName></author><author><firstName>Jens</firstName><middleNames>P</middleNames><lastName>Dreier</lastName></author><author><firstName>Yvo</firstName><middleNames>B W E M</middleNames><lastName>Roos</lastName></author></authors></publication></public

ations><cites></cites></citation>}. GOS was dichotomised into favorable outcome (GOS 4&5) and unfavorable (GOS 1-3).

Data entry including outcome assessment at discharge was done by neurovascular clinical specialist nurses.

Statistical analysis was performed using Wizard 1.8.17. Univariate analysis was performed for all categories to determine significant differences between patients making a favorable recovery and those not. Categorical variables were assessed using the Chi-squared test.

Distribution of continuous data was tested using the Shapiro-Wilk test. The t-test was used for normally distributed data and Mann-Whitney or Kruskal-Wallis for data that was not normally distributed. Case mix adjustment using binary logistic regression was then performed to determine the odds of achieving a unfavorable outcome or being discharged home with variables identified to be significant on univariate analysis. Significance was defined as  $p < 0.05$ .

## **Results:**

Of 4634 patients recorded on the UK and Ireland database, 3341 patients were recorded to have an intracranial aneurysm and were eligible for this analysis. The median age at presentation of the cohort was 55 years of age, and the majority of patients were female.

Although most patients presented in good grade, almost a quarter of patients ( $n=854$  (24.9%)) presented in poor grade. Most patients had anterior circulation aneurysms, three quarters of patients were treated by endovascular coiling, and over 1/3 ( $n=1058$  (34.2%)) of patients required some form of a CSF diversion procedure. CSF diversion was in the form of an external ventricular drain in the majority ( $809/1058$  (83%)).

The majority of patients ( $n=2385$  (71.4%)) had made a favorable recovery discharge, and most, ( $n=1836$  (54.4.%)) were discharged home directly from the neurosciences center after a median hospital stay of 15 days (see table 1).



Patients that had an unfavorable outcome at discharge were significantly older, more often presented in poor clinical grade, were more likely to be smokers, and have a history of hypertension and/or IHD at presentation. The incidence of re-bleed, need for CSF diversion and CSF infection were significantly higher in patients with an unfavorable outcome. (table 2).

The time interval between admission and securing of aneurysm was not significantly longer for patients in the favorable group compared to patients in the unfavorable group.

Significant factors from the univariate analysis were entered into a multiple regression model to determine the independent predictors of an unfavorable outcome at discharge and the adjusted odds of getting home.

Previously well accepted independent predictors of negative outcome such as age, WFNS grade, pre-operative re-bleed and lack of treatment were confirmed in this cohort. (see table 3). Increasing age, worse grade at presentation, pre operative re-bleed, no treatment were also factors which significantly reduced the odds of being discharged home.

The model also identified that patients that had a CSF diversion procedure were 3.25 fold more likely to have an unfavorable outcome independent of age, WFNS grade, pre operative re-bleed, no treatment. The adjusted odds of being discharged home was also significantly lower in patients that had a CSF diversion procedure. The reason for this is not clear, but given that the adjusted odds of getting home were significantly lower (OR 0.31 CI 0.15-0.70,  $P=0.005$ ) for patients that had a definite CSF infection suggests that CSF infection may be a key contributor. (Table 4).

## **Discussion**

We have shown that increasing age, WFNS grade at presentation, preoperative re-bleed, and DCI remain independent predictors of an unfavorable outcome in patients presenting with aSAH. We have also observed that the need for CSF diversion is associated with a 3.25-fold

adjusted odds of an unfavorable outcome at discharge. This data is important as understanding why the need for CSF diversion increases the risk of a poor outcome is likely to drive further improvements in outcome after aSAH particularly as factors such as age or injury severity cannot be modified. Definite CSF infection is an independent negative predictor of being discharge home and is a likely cause of poor outcomes associated with CSF diversion.

Pre operatively re-bleeding is a well accepted predictor of outcome in many studies and remains a challenge in this contemporary real world population of aSAH patients{ ADDIN PAPERS2\_CITATIONS <citation><uuid>88B58D9B-2568-4FD9-827E-09CE0A882C89</uuid><priority>4</priority><publications><publication><uuid>F7D972FD-BCFD-4EF9-B59E-2A7B34742991</uuid><volume>9</volume><doi>10.1371/journal.pone.0099536</doi><startpage>e99536</startpage><publication\_date>99201406091200000000222000</publication\_date><url>http://dx.plos.org/10.1371/journal.pone.0099536</url><citekey>Tang:2014il</citekey><type>400</type><title>Risk Factors for Rebleeding of Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis</title><number>6</number><subtype>400</subtype><endpage>6</endpage><bundle><publication><title>PloS one</title><type>-100</type><subtype>-100</subtype><uuid>ECC55E26-5C2E-4BB6-A835-489E731989F7</uuid></publication></bundle><authors><author><firstName>Chao</firstName><lastName>Tang</lastName></author><author><firstName>Tian-Song</firstName><lastName>Zhang</lastName></author><author><firstName>Liang-Fu</firstName><lastName>Zhou</lastName></author></authors><editors><author><firstName>Jinglu</firstName><lastName>Ai</lastName></author></editors></publication></publications><cites></cites></citation>}. Early treatment of ruptured aneurysm is now

considered the norm to reduce re-bleeding and this is reflected in this series where the median time to treat was one day. Ultra early treatment strategies have been proposed by a number of SAH treating specialists although this has not been shown to be any better than a more pragmatic 'treat as early as possible' approach in some studies{ ADDIN

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Group</publisher><institution>Department of Neurosurgery, The Royal Melbourne Hospital, Victoria, Australia.

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ublications><cites></cites></citation>} In trying to stop pre operative re-bleeding it remains

important to understand the population in which it occurs. Whilst critical to avoid re-

hemorrhage in good grade patients, re-bleed in poor grade patients may be the result of a

purposeful treatment strategy driven by the clinical presentation and acute pathophysiological

changes. Equally it has been shown in contemporary studies that most re-bleeds occur within 6 hours of aneurysm rupture and given that in the majority of health care systems patients require transferring to specialist centers even if practical to deliver an ultra early intervention approach may not be enough{ ADDIN PAPERS2\_CITATIONS

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DCI is another well accepted factor that contributes to poor outcome{ ADDIN

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ites></cites></citation>}. Over time a number of challenges including agreeing on a clinical definition of the syndrome of secondary deterioration has been agreed and there is now better understanding of the pathophysiology of secondary deterioration which may help in

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/firstName><lastName>Vail</lastName></author><author><firstName>H</firstName><mi  
ddleNames>C</middleNames><lastName>Patel</lastName></author></authors></publicati  
on></publications><cites></cites></citation>} It is these secondary factors that need to be  
addressed with a view to minimizing harm and improving outcomes as some could be  
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There is currently no national or international consensus to guide the use of CSF diversion in patients with an aSAH, and there is a wide variable range of practice reported. { ADDIN

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ations><cites></cites></citation>}. The practice of routine use of CSF diversion is most noticeable in poor grade SAH patients where several centers have a blanket approach in using CSF diversion{ ADDIN PAPERS2\_CITATIONS <citation><uuid>320427AB-1D96-42E7-B46D-

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argument for this approach is based on observations that poor grade patients can improve clinical grade after drainage of CSF and achieve outcomes similar to those that present in

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also anecdotal evidence that CSF diversion can improve cerebral oxygenation and reduce the DCI{ ADDIN PAPERS2\_CITATIONS <citation><uuid>4D7AD837-C09C-4029-B7EB-D2CAC2EBCF34</uuid><priority>18</priority><publications><publication><uuid>7427EAE0-553B-42EF-AA28-

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ations><cites></cites></citation>}. However, not all patients with poor grade SAH have

ventriculomegaly, and even these patients can improve clinical grade with time without need

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uthor></authors></publication></publications><cites></cites></citation>}. Where there is

evidence of hydrocephalus from the outset, which Lu et al observed in about 17.8% of

patients, almost 30% recovered, one third remained stable with only 37% of patients with

radiological and clinical hydrocephalus required intervention { ADDIN

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consecutive series of 473 patients described by Hasan et al, 91 (19%) had hydrocephalus on the initial computed tomogram{ ADDIN PAPERS2\_CITATIONS

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ations><cites></cites></citation>}. Consciousness was unimpaired in 25 of the 91 (28%) and  
thirty-eight (8%) of all 473 patients subsequently showed clinical deterioration because of  
acute hydrocephalus. Of the 66 patients with acute hydrocephalus and impaired  
consciousness on admission, 26 (39%) spontaneously improved within 24 hours and CSF  
diversion was required in 32 (31%). Overall CSF diversion was required in 7% of all 473  
patients compared to the 25% of patients as described in this series{ ADDIN

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ations><cites></cites></citation>}. These observations suggest that routine CSF drainage is not always necessary and decisions should be made on a case by case basis rather than according to a set protocol even for poor grade patients.

Our data represent the largest contemporary aSAH patient database. The patient episodes have been accumulated over a short space of time from multiple centers in the United Kingdom. It is data reflective of current clinical practice where about one quarter of patients are in poor grade at presentation, and most patients are treated early and by endovascular coiling. Outcomes at discharge were not available in only 4% of patients and overall only 5% of our data was missing. Our study is limited in that the data from each center has not been independently validated, although data is collected by clinical nurse specialists that are well versed with the SAH patient journey, and collected according to pre set definitions. Only 4 centers have provided data on consecutive patients over the 5 year period although once centers started contributing most (10/14) continued to submit data regularly. Our data is also limited in that outcomes are recorded at discharge whilst most clinical trials report outcomes at 3 months.

## **Summary/Conclusions**

In a large contemporary series of aSAH we have shown that potentially modifiable risk factors of pre operative re-bleeding and DCI remain barriers to favorable outcomes.

Understanding the reasons why patients requiring CSF diversion have higher adjusted odds of a poor outcome at discharge needs to be studied further.

### **Declaration of Interest**

None

### **Acknowledgements**

The acknowledgments section lists all substantive contributions of individuals. Authors should obtain written, signed permission from all individuals who are listed in the "Acknowledgments" section of the manuscript, because readers may infer their endorsement of data and conclusions. These permissions must be provided to the Editorial Office. Please see the { HYPERLINK "http://www.ahajournals.org/site/misc/permission.xhtml" }. The corresponding author must mark the following statement on the ONLINE ONLY Copyright Transfer Agreement form or Licensing Agreement, certifying that (1) all persons who have made substantial contributions in the manuscript (e.g., data collection, analysis, or writing or editing assistance), but who do not fulfill authorship criteria, are named with their specific contributions in the Acknowledgments section of the manuscript; (2) all persons named in the Acknowledgments section have provided the corresponding author with written permission to be named in the manuscript; and (3) if an Acknowledgments section is not included, no other persons have made substantial contributions to this manuscript.

### **References.**

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<b>Number of patients with intracranial aneurysms</b>		3341
<b>Median age (IQR)</b>		55(18)
<b>sex (% Female)</b>		68.5%
<b>Median time to treat (days)</b>		1(2)
<b>WFNS</b>	<b>grade 1</b>	1715 (49.7%)
	<b>grade 2</b>	682 (19.8%)
	<b>grade 3</b>	202 (5.8%)
	<b>grade 4</b>	412 (11.9%)
	<b>grade 5</b>	442 (12.8%)
<b>Aneurysm location</b>		
<b>Anterior circulation</b>		83%
<b>Posterior circulation</b>		17%
<b>Treatment</b>		
<b>Endovascular coiling</b>		2600 (75%)
<b>Clipping</b>		596 (17.2%)
<b>Both clipping and coiling</b>		44 (1.3%)
<b>None</b>		225 (6.5%)
<b>Hypertension</b>		1155 (35.6%)
<b>Ischaemic Heart disease</b>		222 (7%)
<b>Smoker</b>		1398(45.2%)
<b>Pre operative re-bleed</b>		133 (4.9%)
<b>Delayed Cerebral Ischaemia</b>		681 (21.7%)
<b>CSF diversion</b>		1058 (34.2%)
<b>CSF sepsis ( definate)</b>		171(5.6%)
<b>LOS (IQR)</b>		15 (14)
<b>GOS at discharge</b>		
<b>Favourable</b>		2385 (71.4%)
<b>Unfavorable</b>		956 (28.6%)
<b>Discharge destination</b>		
<b>Home</b>		1836 (54.4%)
<b>District general</b>		748 (22.2%)
<b>Rehabilitation</b>		421 (12.5%)
<b>Dead</b>		369 (10.9%)

Table 1: Overall demographics and outcomes in patients with aneurysmal SAH.

	Favorable 2385	Unfavorable 956	
<b>Age (median)(IQR)</b>	54 (17)	60 (19)	p<0.001
<b>Sex (%Female)</b>	1540 (67.7)	649 (70.2%)	p=0.168
<b>Time to treat days (Median)(IQR) (Mean (SD))</b>	1(2) 3.2 (0.3)	1 (2) 2.7 (0,4)	p<0.03
<b>WFNS grade 1</b>	1505(63.6%)	166 (17.5%)	p<0.001
<b>WFNS grade 2</b>	490 (20.7%)	160 (16.9%)	
<b>WFNS grade 3</b>	103 (4.4%)	85 (9%)	
<b>WFNS grade 4</b>	178((7.5%)	208 (21.9%)	
<b>WFNS grade 5</b>	91 (3.8%)	330 (34.8%)	
<b>Hypertension</b>	749 (32.7)	362 (44.1%)	p<0.001
<b>Ischaemic Heart disease</b>	135 (6%)	78 ( 10%)	p<0.001
<b>Smoker</b>	1040 (46.4%)	310 (42.6%)	p=0.08
<b>Site of Aneurysm</b>			p=0.09
<b>anterior</b>	1997 (87.4%)	781 (85.2%)	
<b>posterior</b>	288 (12.6%)	136 (14.8%)	
<b>Treatment</b>			p<0.001
<b>Endovascular</b>	1881 (79.1%)	622 (65.5%)	
<b>Surgical</b>	397 (16.7%)	163 (17.2%)	
<b>Both</b>	73 ( 3.1%)	16 (1.7%)	
<b>No intervention</b>	23 (1.1%)	149 ( 15.7%)	
<b>Pre operative re-bleed (%) (95% CI)</b>	40 (1.9%) (1.4-2.6)	88 (10.7%) (8.8-13)	p<0.001
<b>Delayed Cerebral Ischaemia (%) (95% CI)</b>	381 (17.9%) (16.3-19.5)	269 (31.2%) (28.2-34.4)	p<0.001
<b>CSF diversion (%) (95% CI)</b>	436 (20.7%) (19-22.4)	548 (64.2%) (61-.67.4)	p<0.001
<b>CSF infection</b>			p<0.001
<b>definate</b>	29 (1.4%)	48 (5.7%)	
<b>probable</b>	30 (1.4%)	56 (6.7%)	
<b>Length of stay (median)(IQR)</b>	14 (11)	22 (30)	p<0.001

Table 2: Baseline characteristics of patients that made a favorable recovery vs those that did not.

Table 3: The adjusted odds of an unfavorable outcome.

Explanatory variable	Odds Ratio	95% CI	p value
Age	1.04	1.03-1.05	p<0.001
WFNS grade	1.84	1.91-2.22	p<0.001
Pre-op re-bleed	7.23	4.48-12.30	p<0.001
DCI	2.23	1.72-2.83	p<0.001
Hypertension	0.95	0.73-1.14	p=0.661
IHD	1.02	0.65-1.40	p=0.954
Treatment	0.20	0.64-1.08	p<0.001
CSF diversion	3.52	2.58-4.09	p<0.001
CSF infection			
definite	1.65	0.90-2.78	p=0.107
probable	1.36	0.64-2.03	p=0.656

Table 4: The adjusted odds of getting home

Explanatory variable	Odds Ratio	95% CI	p value
Age	0.95	0.94-0.96	p<0.001
WFNS grade	0.44	0.40-0.47	p<0.001
Pre-op re-bleed	0.18	0.11-0.32	p<0.001
DCI	0.40	0.30-0.47	p<0.001
Hypertension	1.24	0.92-1.43	p=0.661
History of IHD	1.22	1.02-1.51	p=0.954
Treatment	0.53	0.42-0.67	p<0.001
CSF diversion	0.34	0.15-0.67	p<0.001
CSF infection			
definite	0.31	0.15-0.70	p=0.004
probable	0.78	0.39-1.54	p=0.473